The Direction of Innovation of Antibacterial Agents in Preventing Wounds Infection: A Systematic Review

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ABSTRACT
Skin is a part of the body that serves to protect other body parts in it. Wounds are a disruption of skin integrity, as well as a threat to the security of the body, especially from the risk of infection. The current management of infection has complicated problems that have not been resolved properly, namely bacterial resistance to antibiotics. The discovery of new anti-bacterial substances is one of the keys to preventing delays in wound healing and various complications in wound healing. This type of research is a systematic review, by analysing journals published in 2016-2021 from the science direct and PubMed databases. There were 8 articles analysed to determine the presence of new anti-bacterial active substances that were clinically tested. The results of the analysis showed that there were 6 articles in clinical trials that showed positive results in treating and preventing infection, and 2 with the opposite result. All articles analysed did not present a review of the new antibacterial agent. The researcher concludes that the development of the discovery of new antibacterial substances is slow, because there are no clinical trials of new antibacterial active ingredients in wound dressings in the 2016-2021 period, although there is one prospective method to be developed, namely bacterial binding dressing.

Keywords: Skin; Antibacterial Agents; Wounds Infection

1. INTRODUCTION

Wound is a state of disturbance to the integrity of the skin [1]. The function of the skin is to protect the body from infection. This function is carried out on the principle of a physical barrier, which is played by the 3 main layers of the skin. This layer includes the epidermis, dermis and sub dermis [2]. In addition to the physical barrier, the skin plays a role in preventing infection through immune surveillance mechanisms [3].After an injury occurs, the skin performs the function of preventing infection through the inflammatory process[4] [5]. Damaged skin integrity, which occurs in one or all layers of the skin, increases the risk of infection in the body of the injured person. In 2014, based on data from Medicare which serves patients in various countries, it shows that there are about 5.5 million patients with wound infections [6].

Infections in the wound cause various impacts on the patient's life in the form of a long treatment period, patient discomfort, physical complications and economic impacts [7]. Infections in postoperative wounds are the top 3 contributing factors to patient mortality[8] [9]. The impact of a very fatal infection, requires the right resolution strategy. Infection prevention strategies have been developed by many researchers. Research that has addressed the problem of infection includes: the use of antibiotics, the use of antiseptics, the use of antibacterial dressings and the reduction of the bacterial burden through debridement [10], and supported by good infection recognition [11]. The problem of infection prevention that is currently the focus of researchers' attention is the emergence of the phenomenon of multidrug resistant bacteria (MDR) [12], [13]. Research has been carried out by many researchers, such as modifying hydrogel dressings [14], foam dressing [15] with various anti-bacterial substances antibiotic, silver and other antibacterial agents. However, from several studies in the last 5 years, there are no studies that utilize new anti-bacterial substances. In a clinical study found cases of bacteria resistant to antibiotics whose samples were isolated from wounds [16]. The incidence of MDR has an impact on treatment costs, length of treatment, and risk of death [17]. A strategy is needed to deal with this phenomenon, namely by using antibiotics wisely and innovations and new antibacterial discoveries [18].

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Strategies that can be implemented in dealing with wound infections are identification of the cause of the wound, debridement, drainage and the use of antibacterial dressings [19], administration of systemic antibiotics and anti-inflammatory agents [20].

There have been many research articles and review articles that discuss the discovery and testing of antibacterial. There are quite recent studies such as Quorum-sensing inhibitors, Nano therapy, macrophages, antibodies, and essential oils [18]. Research on antibacterial wound dressings in the clinical realm has also been carried out. However, based on our literature study, there are no review articles that focus their studies on testing new antibacterial base materials that are clinically applied to wound dressings. In this article, a literature review will be presented with the aim of presenting a study of the history of the discovery of active substances and the effectiveness of infection prevention.

2. METHOD

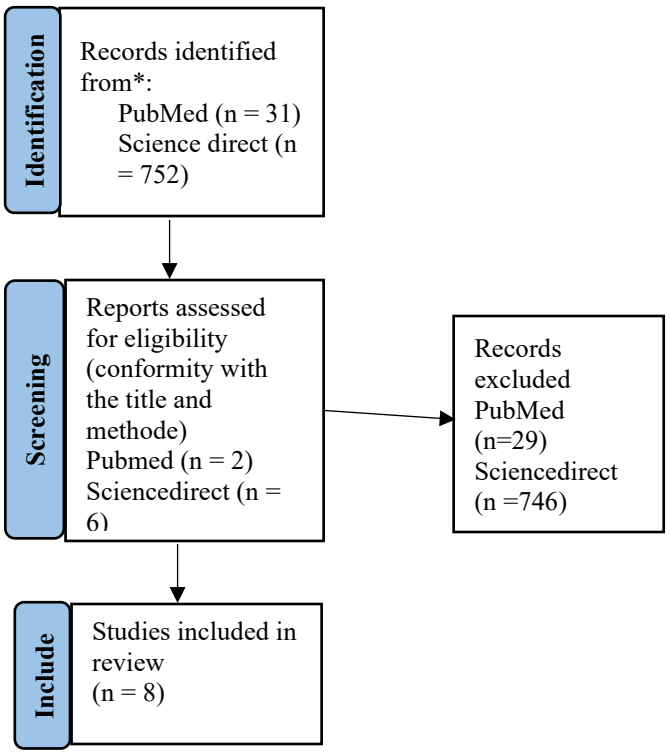

Figure 1 Prisma Flowchart (processed by the authors)

We search for articles on 27 July 2021 at 10:45 p.m. from PubMed and scientific direct databases with the keywords "antibacterial wound dressing AND randomized controlled trial". The search was carried out on articles published in the database in the last 5 years. From PubMed database found 31 articles and sciencedirect 752 articles. The article selection done according to the conformity of title and abstract. The article must contain the clinical research design and involve testing wound dressings containing active anti-bacterial substances. After the selection, 2 appropriate articles were obtained from the PubMed database and 6 articles from the scientific direct database. Furthermore, the 8 articles that were obtained were analysed in depth with a focus on the reliability of antibacterial dressing products in infection management and the novelty of antibacterial dressing raw materials. Each research personnel have the task of Sodiq Kamal, conducting journal searches and compiling publication manuscripts, Estrin Handayani conducting research designs, Alfian Syarifuddin conducting final checks.

3. RESULT AND DISCUSSION

All articles discussed in this literature review do not use antibacterial raw materials in new wound dressings. There are articles that modify the carrier medium for antibacterial substances only. There are also articles that test formulations of traditional herbal medicines, but the active substances in them are by no means new. In fact, there is an article that examines the active substance in the form of an antibiotic that actually has the potential to

cause resistant bacteria. Meanwhile, the demand for the MDR phenomenon is to find new antibacterial [21].

Testing of antibacterial substances in the article under review showed that 6 active substances had an anti-bacterial effect and one antibacterial substance was not effective in preventing infection in surgical wounds. There are two antibacterial substances that have silver components, namely SSD and silver Nano crystalline. One article uses herbal ingredients, namely GM. One article uses a material that acts as a barrier to wounds, namely silicone. One anti-bacterial substance tested using an antiseptic is acetic acid. One article uses a biological material, namely a bacteriophage. And the last one is an article with a material that is bacterial binding dressing, using DACC.

Table 1 Findings

No	Researchers	Findings	Gap Analysis
1	Akita, S. et. Al. (2016)	The Silver Sulfadiazine (SSD) in hydrocolloid dressing can be a barrier for wounds.	The SSD used in this study is not a new antibacterial agent.
2	Madhusudhan, VL (2016)	acetic acid is effective in removing P. aeruginosa from chronic wounds.	Acetic acid is not an antibacterial substance which is a new discovery
3	Jault, P., et.al. (2018)	Cocktail of natural lytic anti-P aeruginosa bacteriophages PP1131; 1×10^6 plaque-forming units [PFU] per mL reduces bacterial burden.	Cocktail of natural lytic anti-P aeruginosa bacteriophages PP1131 is not an invention in the last 5 years
4	Ahmad, HS. Et.al. (2018)	Mupirocin is not effective in preventing infection in surgical wounds.	Mupirocin is not a new antibacterial agent in the last five years
5	Stanirowski, PJ et al (2019)	The use of dialkylcarbamoyl chloride (DACC) is able to prevent infection in wounds.	DACC is not a new antibacterial substance that has been discovered in the last five years.
6	Karlsson, M. et al (2019)	Faster wound healing with the use of silver-foam group.	Silver Nano crystalline (SNC) is not a new anti-bacterial agent
7	Benedetto, AV et al (2020)	Topical silicone gel was able to reduce the incidence of dermatitis, but it was not significant in preventing the incidence of infection.	Silicone used in this study is not a new antibacterial agent
8	Sanpinit, S., et.al(2020)	Garcinia mangostana, Oryza sativa, Curcuma longa, and Areca catechu (Ya-Samarn-Phlae (YaSP)) have antibacterial and antibiofilm activities.	The main substance in YaSP, namely Garcinia mangostana is not a new discovery, although clinical trials of YaSP are scientific tests that were only carried out in 2019

Silver has been known for a long time as an anti-bacterial. In fact, silver has been used since ancient Egypt [22]·[23]. There are various forms of silver. In this review, SSD and SNC will be studied. SSD is a topical therapy that is often used for burn therapy. The term SSD was first used by Fox in 1968, with the conclusion that the use of SSD in mice could reduce the mortality of burn models in mice [24]. The first clinical trial was conducted by Lowbury in 1971 with the conclusion that SSD can with daily repetitions can provide better quality burn protection [25]. Good results from clinical trials of SSDs are inconsistent, a review conducted by Miller shows that there is not sufficient scientific evidence to support that SSDs can reduce mortality, prevent infection and accelerate wound healing [26]. In addition, there are concerns about the use of SSD, namely the potential for sensitivity, haemolytic anaemia, hyperbilirubinemia, methemoglobinemia, anaphylaxis, toxic epidermal necrolysis, Stevens-Johnson syndrome, agranulocytosis, leukopenia, and bacterial resistance [27].

SNC has an anti-bacterial effect like other silver products. However, SNC has advantages that are not shared by others, namely inactivation of silver by proteins and anions in wound fluid. This causes the side effects of silver to be controlled [28]. Until now, researchers have not found literature that discusses the side effects of SNC.

Acetic acid is a type of antiseptic. The use of this antiseptic is effective for eliminating Pseudomonas aeruginosa in wounds. The use of acetic acid can also minimize the irrational use of antibiotics and lead to resistance. The first study using acetic acid was in patients with gangrene with satisfactory results[30]. Acetic acid has no side effects [29]. Although acetic acid is not a new antibacterial agent, it has the potential to be a solution for wound infections.

Bacteriophage (BP) is a virus that infects bacteria [31]. Research on BP was first conducted in However, research on the phenomenon of BP itself has been carried out since 1921 by Andre Gratia. The first use of the term BP was in September 1922 by Wilbert C division. The PubMed publication database informs us that research on bacteria themes increased rapidly in 1961. The first clinical trial research was conducted in 1965 by For the treatment of osteomyelitis [32]. Some of the advantages of using BP are that in terms of preventing infection BP can be more effective than antibiotics, BP works specifically and does not infect human cells, BP can destroy biofilms which are obstacles in treating infection in wounds, and it is cheap [33]. Limitations in the application and development of BP are because the identification of BP requires complex and lengthy research, the potential for the phenomenon of bacteria resistant to BP, suspected of contributing to antibiotic

resistance, the potential for a response by the immune system so that it can reduce its effectiveness [33].

Mupirocin is a type of antibiotic. Mupirocin was first clinically tested with wound cases in 1985 with the conclusion that mupirocin was effective in reducing the number of bacteria in surgical wounds [34]. Accordingly, mupirocin ointment is more effective in treating skin infections than systemic antibiotics [35]. However, studies over the last decade have found resistance to mupirocin [36], [37].

Silicone dressing is a dressing that is coated by silicon which acts as an adhesive or as a layer that is in direct contact with the wound. the first study using silicon in clinical trials with wound healing objects succeeded in providing a good healing effect, the research was conducted in 1984[38]. Silicone dressings affect the remodelling phase by helping collagen maturation [39]. This has an effect on preventing scar formation in wounds [40]. Other studies have shown that this silicone plays a role in infection control [41]. Silicone has a protective effect in preventing infection in burns [42]. In addition to the various advantages of silicon in infection control, it also has a weakness, namely that it cannot be applied to large wound areas and has the potential to cause irritation in hot conditions[40].

YaSP is a traditional Thai polyhedral formula for the treatment of chronic wounds[43]. The research that tested YaSP is new scientific research conducted in the last 5 years. However, the main raw material, namely Garcinia mangostana (GM), is not a new anti-bacterial substance. The first study of GM was conducted in 1979[44]. GM alone produced significant antiulcer activity in rats. based on PubMed data base, research using GM is increasing rapidly in 2007. The first clinical trial was in 2007 and concluded that GM fruit peel extract could potentially prevent bad breath in cases of gingivitis[45].

There is very little published history of research using DACC. DACC is used to coat wound dressing material to form Bacterial binding dressing (BBD) [46]. Research aimed at characterizing dialkylcarbamoyl has been carried out since 1973[47]. The use of DACC in the first clinical trial in 2011, found that the use of DACC was effective in reducing bacterial burden[48], to prevent infection in surgical wounds in patients with Sectio caesaria (SC) [49].

According to the researcher's opinion, BBD is a wound infection prevention strategy that is still very broad to be explored and developed. BBD is able to minimize the negative impacts that arise such as cytotoxicity and tissue growth inhibition[50]. Apart from using DACC, another method that can be used to create BBD is plasma treated material. Plasma has the potential to affect the electrical properties of a material. Referring to a general concept of the adhesion of bacteria to a material, bacteria with a negative fabric will tend to adhere to a material with a positive charge and vice versa [51]. Thus, the plasma treated material method has the potential to be used as a method to form new BBD.

4. CONCLUSION

Findings Our literature study on articles from clinical research found that there were no clinical trials of new antibacterial wound dressing raw materials for the last 5 years. This research is very important in providing direction for further research about development antibacterial dressing. In order to answer the challenge of the emergence of new resistant bacteria, it is necessary to avoid the use of antibiotics as antibacterial dressings. The recommendation from our findings is that researchers are encouraged to conduct studies in the development of bacterial binding dressings. Research on bacterial binding dressings is prospective, because it will not cause bacterial resistance and more intensive research still needs to be developed.

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